Int J Clin Exp Med 2016;9(6):9791-9798
www.ijcem.com /ISSN:1940-5901/IJCEM0023905

Review Article

Progress of positron emission tomography/computed tomography in the management of nasopharyngeal carcinoma

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Received January 12, 2016; Accepted March 27, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: Nasopharyngeal carcinoma (NPC) is an aggressive malignancy in the head and neck. South China is one of the areas with the highest occurrence of this disease. Radiotherapy is the primary therapeutic modality for NPC. Early accurate diagnosis and staging provide important value to NPC treatment. Nuclear medical imaging technologies, particularly positron emission tomography/computed tomography (PET-CT), have shown significant application value in the clinical diagnosis, staging, treatment, and prognosis of NPC in recent years. This review summarizes the recent advances in the development of PET-CT in the diagnosis, staging, treatment, and prognosis of NPC.

Keywords: Nasopharyngeal carcinoma, PET-CT

Introduction

As an aggressive malignancy in the head and neck, nasopharyngeal carcinoma (NPC) presents early symptoms that are not obvious, but this disease exhibits high-metastatic potential. At the time of diagnosis, > 60% of NPC patients showed locally advanced disease, and approximately 5%-8% of these patients presented distant metastasis [1, 2]. In 2012, up to 86,000 new cases of NPC were diagnosed worldwide; only 6% were detected in Europe, and 80% occurred in Asia [3]. China is one of the countries with the highest occurrence of NPC; this country presents an extremely unbalanced epidemiology and geographic distribution, with the highest incidence between 20 and 50 individuals per 100,000 males in Southeast China [4]. Genetic, ethnic, and environmental factors play important roles in the etiology of NPC. Thus, NPC always presents significant racial, regional, and familial aggregation phenomena [5]. In non-endemic areas, the major histological type of NPC is keratinizing squamous-cell carcinoma, whereas > 95% of NPC cases are non-keratinizing carcinoma in endemic areas [6, 7]. Several critical structures are adjacent to the nasopharynx, including the parotid glands, eyes, brain stem, and spinal cord. Given the complexity of anatomical features, characteristics of infiltrative growth, and radiosensitivity, radiotherapy (RT) has become the primary therapeutic modality for early-stage NPC [8]. At the time of diagnosis, most NPC patients presented with stage III or IV of the disease and displayed poor prognosis [9]. The five-year overall survival rates ranged from 70.0% to 81.7% [10-14]. Recurrence and metastasis often occurred after treatment of locally advanced NPC. The primary failure model was distant metastasis, followed by local regional recurrence and regional lymph node metastasis [15, 16]. To improve the efficacy of treatment, NPC relies on early diagnosis and reasonable treatment.

To date, computed tomography (CT) and magnetic resonance imaging (MRI) are mainly used to display pharyngeal soft tissues, the nasopharyngeal cavity, and the scope of tumor lesions. Both methods provide intuitive imaging for RT or surgery. The advantages of MRI include its high-resolution images of soft tissues and its multidirectional and multiple-parameter imaging. MRI can demonstrate parapharyngeal

space, perineural tumor spread, and bone marrow involvement. Moreover, MRI can show the involvement of adjacent structures, such as paranasal sinuses. Both CT and MRI depend on the size and shape of the lesions, and their specificity is low. Pathological examination is the most feasible way to diagnose local residual and recurrent tumors of NPC, but it is difficult to conduct when the tumors are located in the submucosa or relapsed in deep positions [17].

Nuclear medical imaging is a functional and molecular imaging technique, which involves positron emission tomography (PET)/computed tomography (CT) and single-photon emission computed tomography (SPECT) imaging. This technique plays an important role in the diagnosis, staging, treatment, and prognosis of NPC. The present review summarizes the recent advances in the development of nuclear medical imaging in the diagnosis, staging, treatment, and prognosis of NPC.

^{18}F-FDG PET/CT in NPC diagnosis and treatment

Principle of FDG PET/CT

Fluorodeoxyglucose (FDG) is a glucose analog that has been labeled by fluorine-18 (^{18}F). ^{18}F-FDG is the most widely used PET radiotracer [18]; with the same mechanism as glucose, FDG is absorbed by cells depending on the hexokinase and glucose transporters and then rapidly excreted by renal tissues [19]. The radioactive half-life of ^{18}F is 110 min. ^{18}F emits a positron, which counters an electron of the tumor cells and is converted into two 511 KeV gamma photons (annihilate radiation) in the opposite direction. The two gamma photons are detected by the detector of PET, and the signals are converted into metabolic functional imaging. FDG is a safe radioactive drug with no pharmacological adverse reactions, as evidenced by numerous patients that have used this drug [20]. PET/CT performs functional and morphological imaging in the same process by combining PET and CT in one imaging device.

^{18}F-FDG PET/CT imaging reflects human tissues at the molecular level of physiological, pathological, biochemical, and metabolic changes.

^{18}F-FDG PET/CT plays an important role in the treatment and management of NPC. ^{18}F-FDG PET/CT fundamentally addresses the limitation regarding the vagueness of anatomical structures on nuclear medical images. Simultaneously, nuclear medical imaging by X-ray attenuation correction significantly improves the accuracy of diagnosis and realizes the complementary advantages of information on molecular metabolism and anatomy.

Staging

As the basis of clinical treatment, accurate staging directly influences the efficacy and prognosis. Abnormal glucose metabolism is usually detected in NPC lesions. ^{18}F-FDG PET/CT imaging results present more apparent characteristics. CT mainly shows the nasopharyngeal mass lesions or localized thickening of soft tissues, whereas PET displays the corresponding active and high metabolism. Previous studies indicated that ^{18}F-FDG PET/CT provide high application value in the diagnosis of NPC primary tumors, cervical lymph nodes, and/or distant metastases [21-25].

Vellayappan et al. [26] performed a meta-analysis to study the accuracy of ^{18}F-^{18}F-FDG PET/CT in the staging of NPC, and their research involved 851 patients from 15 relevant studies. The combined sensitivity in the T, N, and M classification was 0.77 (95% confidence interval, CI: 0.59-0.95), 0.84 (95% CI: 0.76-0.91), and 0.87 (95% CI: 0.74-1.00), respectively. The combined specificity in the N and M classification was 0.90 (95% CI: 0.83-0.97) and 0.98 (95% CI: 0.96-1.00), correspondingly. The diagnostic odds ratios (DORs) in the N and M classification were 82.4 (95% CI: 23.2-292.6) and 120.9 (95% CI: 43.0-340.0), respectively. The results showed that FDG-PET/CT presented good accuracy in the N and M classification for the staging of NPC [26].

The accurate judgment of the lymph node metastasis of NPC is important because of its high metastasis rate. The conventional work-up (CWU) CT/MRI mainly evaluated the lymph nodes according to their size, but the metastatic lymph nodes and reactive nodes are difficult to distinguish based on the CT/MRI size and morphological criteria [27]; thus, false positives or false negatives may appear. ^{18}F-FDG PET/CT can more accurately determine lymph node properties based on glucose metabolism. Compared with CT/MRI, ^{18}F-FDG PET/CT can detect smaller positive lymph nodes. Numerous studies indicated that PET/CT is superior to

other modalities (CT or MRI) in the initial staging because of the discovery of unexpected cervical lymph nodes, which were not detected by the CWU [21, 28-30]. A meta-analysis by Shen et al. [31], which included 20 studies of 7 databases (4 in English and 3 in Chinese) from January 1990 to June 2013, indicated that PET or PET/CT demonstrates good diagnostic performance for detecting lymph nodes in NPC patients; the combined sensitivity of PET or PET/CT in N and M classification was 0.89 [95% CI, 0.86-0.91] and 0.96 (95% CI, 0.95-0.96), respectively [31].

RT of NPC demonstrates good effects, although the incidence rate of distant metastases is high. The accurate description of distant metastasis is important for the treatment planning of NPC. The CWU for distant metastasis detection of NPC includes a bone scan, chest X-ray, and abdominal ultrasound examination. However, all these methods face significant limitations. Early bone marrow metastases are not easily detected by bone scan. Similarly, early mediastinal or lung metastases are difficult to be detected by chest X-ray. Ultrasound cannot effectively distinguish between benign and malignant lesions because the results of ultrasound technology mainly rely on the operator.

Previous studies suggest that ^{18}F-FDG PET/CT is superior to CWU for detecting distant metastases [31-36]. Chang et al. [36] reported a systematic review and meta-analysis on the accuracy of FDG-PET and FDG-PET/CT in the M staging of NPC, which included eight studies from October 1996 to September 2011. The sensitivity was 0.83 (95% CI, 0.77-0.88), whereas the specificity was 0.97 (95% CI, 0.95-0.98); the positive likelihood ratio was 23.38 (95% CI, 16.22-33.69), and the negative likelihood ratio was 0.19 (95% CI, 0.13-0.25). Their results showed that FDG-PET or PET/CT demonstrates good diagnostic efficiency in detecting distant metastases of NPC [36]. Lin et al. [37] reported the efficiency of detecting distant metastasis of NPC by PET/CT and CWU. A total of 514 patients were randomly divided into two groups: 216 patients in the PET/CT group and 298 patients in the CWU group. The sensitivity and specificity between the two groups were not statistically significant, but the numbers of patients with multiple organ metastases and multiple distant metastases were higher in the PET/CT group than in the CWU group ($P < 0.05$). These results showed that PET/CT is superior to CWU for detecting the distant metastasis of NPC [37].

Radiotherapy treatment planning

^{18}F-FDG PET/CT plays an increasingly important role in the cancer imaging of RT planning, and its positive effects have been reported [30, 38-40]. The sensitivity and contrast resolution of PET/CT are superior to the anatomical imaging techniques in the delineation of target volumes and organs at risk, with which RT planning can be optimized [41]. Several studies suggest that PET-CT exerts a significant effect on the gross tumor volume (GTV). Previous research indicated that the GTV delineated by PET/CT is smaller than that delineated by CWU [42-45].

Further studies on ^{18}F-FDG PET-CT for RT planning can improve the dose-escalation RT for NPC to enhance the therapeutic efficacy and reduce toxicity [30, 40, 42, 46]. Wang et al. [47] conducted a randomized pilot trial on PET-guided dose-escalation RT for chemoradiotherapy of locally advanced NPC. The results suggested that the PET/CT-guided dose-escalation radiotherapy for locally advanced NPC is superior to conventional chemoradiotherapy [47].

Treatment response assessment

Accurate response assessment is important in the treatment of NPC patients. At present, treatment response assessment of patients with NPC is often based on the radiographic changes in tumor size or the alterations of clinical symptoms. The morphological changes of tumors after treatment often lag behind tumor cell death. Although the tumor mass narrowed after treatment, a certain number of tumor cells remained alive. Therefore, CWU methods cannot evaluate the treatment response in a timely and accurate manner. PET/CT can provide a reliable basis for early assessment after treatment or tumor metabolism to evaluate the tumor remnants at the clinical and subclinical levels. Many studies have indicated that PET/CT imaging can be effective for NPC treatment response evaluation [31, 48-49]. Yuan et al. [50] reported a study on the early evaluation of radiotherapeutic effects of NPC xenografts in nude mice via ^{18}F-FDG PET-CT. The average death ratio was significant on day 6 after radiotherapy and at the other time points ($P < 0.05$)

[50]. Su et al. [51] suggested that the maximum standard uptake value (SUV_{max}) of the primary tumor before treatment is an independent predictor of tumor response in NPC.

Prognostic significance of PET-CT

Although NPC is highly sensitive to radiation, local recurrence and distant metastasis are still the major modes of failure in NPC patients [52]. Thus, the search for prognostic factors and the optimization of individualized treatment are particularly important for NPC patients. Numerous studies showed that the standard uptake value (SUV), metabolic tumor volume (MTV), and total lesion glucose (TLG) are useful predictive factors for NPC patients [53-57]. Shi et al. [58] used ^{18}F-FDG PET-CT parameters to predict distant metastasis for NPC patients, which included 43 newly diagnosed NPC patients. The parameters were the mean standardized uptake value (SUV_{mean}), maximum standardized uptake value (SUV_{max}), MTV, and TLG of primary tumors and cervical lymph nodes. The results suggested that the total SUV_{max} is an independent predictive factor for distant metastasis [58]. A retrospective study by Yoon et al. [59] reported the prognostic value of MTV in NPC patients. The authors assessed the prognostic factors of MTV2.5, MTV3.0, SUV_{max}, and other factors with the overall survival (OS) by using Kaplan-Meier and Cox regression models. The results indicated that MTVs (particularly MTV2.5 and MTV3.0) can be valuable prognostic factors for predicting long-term survival in NPC patients [59]. Recently, the prognostic value of volume-based PET/CT was studied in NPC patients treated with concurrent chemoradiotherapy (CCRT) [60]. The authors concluded that TLG is a significant independent metabolic prognostic factor of disease-free survival (DFS) in NPC patients treated with CCRT [60]. Other studies suggested that tumor heterogeneity is also a potential predictor of NPC patient survival after treatment [61, 62].

Diagnosis of residual and recurrent tumors

After radiotherapy, chemotherapy, and even targeted therapy, the nasopharyngeal mucosa can appear to display a series of changes, such as fibrosis, loss of tissue planes, edema, scarring, and mucositis. These changes may interfere with the diagnosis of residual and recurrent tumors. PET/CT is a functional imaging technique with high sensitivity and specificity for the diagnosis of residual and recurrent tumors in NPC patients [63]. Some studies showed that PET/CT played an important role in detecting the residual and recurrent tumors in NPC patients [64, 65]. Chen et al. [66] reported the value of FDG PET-CT with pathology in diagnosing residual tumors in NPC patients after radiotherapy. The specificity of FDG PET-CT and MRI and the pathological tumor response in diagnosing residual tumors were 77.3%, 9.1%, and 95.5% ($P < 0.001$), whereas the accuracy rates were 78.9%, 14.9%, and 95.7%, respectively ($P < 0.001$). These results suggest that PET-CT combined with pathological tumor response is beneficial for the early diagnosis of residual nasopharyngeal tumors after radiotherapy [66].

Application of other positron imaging agents in PET/CT

[^{18}F]-3'-Fluoro-3'-deoxythymidine (FLT) is a thymine analogue used as an imaging agent to quantify cellular proliferation and was first reported by Shields in 1998 [67]; the in vitro experiment showed that ^{18}F-FLT is a good substrate for cytosolic thymidine kinase (TK-1). FLT imaging can reflect the activity of TK-1, which is correlated with the number of cells in the S-phase of the cell cycle [68]. Recently, Zheng et al. [69] reported that ^{18}F-FLT micro-PET/CT can predict radiosensitivity in NPC xenografts on nude mice models. Other studies suggested that ^{18}F-FLT PET/CT can provide important prognostic information for NPC patients [70, 71].

Choline (CHO) widely exists in cells, and ^{11}C-CHO is an imaging agent used for various tumors [72, 73]. CHO can be quickly incorporated into tumor cells and converted into phosphorylcholine by phosphorylation. The uptake rate of ^{11}C-CHO by tumor cells directly reflects the synthesis rate of tumor cell membranes. A previous study indicated that ^{11}C-CHO PET/CT can improve the quality of PET/CT in the T staging of NPC [74]. Jiang [75] reported the variability of GTV in NPC based on ^{11}C-CHO and ^{18}F-FDG PET/CT; the results suggested that ^{11}C-CHO PET/CT imaging can be introduced as an important complementary tool to decrease inter-observer variation in GTVs obtained for NPC [75].

Other positron imaging agents, such as ^{68}Ga, also provide important application value in NPC [76, 77].

Conclusion

Nasopharyngeal carcinoma (NPC) is an aggressive malignancy, early accurate diagnosis and staging provide important value to NPC treatment.

The most recent clinical studies support that PET-CT provides benefits in the diagnosis, staging, therapeutic effect monitoring, and prognosis of NPC. PET/CT also faces limitations, such as the metabolism of inflammatory cells and tuberculosis-infected cells, which can cause false-positive results. At present, PET-CT should be combined with other imaging techniques, such as MRI. The combination of these methods may offer important applications in the diagnosis of NPC in installments, as well as the evaluation of curative effects. However, more multicenter, randomized studies and researches such as imaging biomarkers to guide individual treatment are needed in the future.

Disclosure of conflict of interest

None.

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References

[1] Fong KW, Chua EJ, Chua ET, Khoo-Tan HS, Lee KM, Lee KS, Sethi VK, Tan BC, Tan TW, Wee J, Yang TL. Patient profile and survival in 270 computer tomography-staged patients with nasopharyngeal cancer treated at the Singapore General Hospital. Ann Acad Med Singapore 1996; 25: 341-6.

[2] Heng DM, Wee J, Fong KW, Lian LG, Sethi VK, Chua ET, Yang TL, Khoo Tan HS, Lee KS, Lee KM, Tan T, Chua EJ. Prognostic factors in 677 patients in Singapore with nondisseminated nasopharyngeal carcinoma. Cancer 1999; 86: 1912-20.

[3] International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. (2012). Available at: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx (Accessed: 27nd March 2015).

[4] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.

[5] Qu S, Liang ZG, Zhu XD. Advances and challenges in intensity-modulated radiotherapy for nasopharyngeal carcinoma. Asian Pac J Cancer Prev 2015; 16: 1687-92.

[6] Marks JE, Phillips JL, Menck HR. The National Cancer Data Base report on the relationship of race and national origin to the histology of nasopharyngeal carcinoma. Cancer 1998; 83: 582-8.

[7] Chen L, Mao YP, Xie FY, Liu LZ, Sun Y, Tian LL, Lin AH, Li L, Ma J. The seventh edition of the UICC/AJCC staging system for nasopharyngeal carcinoma is prognostically useful for patients treated with intensity-modulated radiotherapy from an endemic area in China. Radiother Oncol 2012; 104: 331-7.

[8] Lee AW, Lin JC, Ng WT. Current management of nasopharyngeal cancer. Semin Radiat Oncol 2012; 22: 233-244.

[9] Cheng SH, Yen KL, Jian JJ, Tsai SY, Chu NM, Leu SY, Chan KY, Tan TD, Cheng JC, Hsieh CY, Huang AT. Examining prognostic factors and patterns of failure in nasopharyngeal carcinoma following concomitant radiotherapy and chemotherapy: impact on future clinical trials. Int J Radiat Oncol Biol Phys 2001; 50: 717-726.

[10] Wu S, Xia B, Han F, Xie R, Song T, Lu L, Yu W, Deng X, He Q, Zhao C, Xie C. Prognostic Nomogram for Patients with Nasopharyngeal Carcinoma after Intensity-Modulated Radiotherapy. PLoS One 2015; 10: e0134491.

[11] Fuwa N, Kodaira T, Daimon T, Yoshizaki T. The long-term outcomes of alternating chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: a multiinstitutional phase II study. Cancer Med 2015; 4: 1186-1195.

[12] Lin SJ, Pan JJ, Han L, Guo Q, Hu C, Zong J, Zhang X, Lu JJ. Update report of nasopharyngeal carcinoma treated with reduced-volume intensity-modulated radiation therapy and hypothesis of the optimal margin. Radiother Oncol 2014; 110: 385-9.

[13] Wu F, Wang R, Lu H, Wei B, Feng G, Li G, Liu M, Yan H, Zhu J, Zhang Y, Hu K. Concurrent chemoradiotherapy in the locoregionally advanced nasopharyngeal carcinoma: Treatment outcomes of a prospective, multicentric clinical study. Radiother Oncol 2014; 112: 106-11.

[14] Wu SY, Wu YH, Yang MW, Hsueh WT, Hsiao JR, Tsai ST, Chang KY, Chang JS, Yen CJ. Comparison of concurrent chemoradiotherapy versus neoadjuvant chemotherapy followed by radiation in patients with advanced nasopharyngeal carcinoma in endemic area: experience of 128 consecutive cases with 5 year follow-up. PLoS One 2014; 14: 787.

[15] Chen JL, Huang YS, Kuo SH, Chen YF, Hong RL, Ko JY, Lou PJ, Tsai CL, Chen WY, Wang CW. Intensity-modulated radiation therapy for T4 nasopharygeal carcinoma. Strahlenther Onkol 2013; 189: 1001-8.
[16] Zeng L, Tian YM, Sun XM, Huang Y, Chen CY, Han F, Liu S, Lan M, Guan Y, Deng XW, Lu TX. Intensity-modulated radiotherapy for stage IVA/IVB nasopharygeal carcinoma. Strahlenther Onkol 2014; 190: 993-1000.
[17] Liu T, Xu W, Yan WL, Ye M, Bai YR, Huang G. FDG-PET, CT, MRI for diagnosis of local residual or recurrent nasopharyngeal carcinoma, which one is the best? A systematic review. Radiother Oncol 2007; 85: 327-35.
[18] Larson SM, Schwartz LH. 18F-FDG PET as a candidate for "qualified biomarker": functional assessment of treatment response in oncology. J Nucl Med 2006; 47: 901-3.
[19] Jones SC, Alavi A, Christman D, Montanez I, Wolf AP, Reivich M. The radiation dosimetry of 2 [F-18]fluoro-2-deoxy-Dglucose in man. J Nucl Med 1982; 23: 613-617.
[20] Silberstein EB. Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. J Nucl Med 1998; 39: 2190-2192.
[21] Mohandas A, Marcus C, Kang H, Truong MT, Subramaniam RM. FDG PET/CT in the management of nasopharyngeal carcinoma. AJR Am J Roentgenol 2014; 203: W146-57.
[22] Yoo J, Henderson S, Walker-Dilks C. Evidence-based guideline recommendations on the use of positron emission tomography imaging in head and neck cancer. Clin Oncol (R Coll Radiol) 2013; 25: e33-66.
[23] Arias F, Chicata V, García-Velloso MJ, Asín G, Uzcanga M, Eito C, Quilez I, Viudez A, Saenz J, Hernández I, Caicedo C, Errasti M, Barrado M, García-Bragado F. Impact of initial FDG PET/CT in the management plan of patients with locally advanced head and neck cancer. Clin Transl Oncol 2015; 17: 139-44.
[24] Lee HS, Kim JS, Roh JL, Choi SH, Nam SY, Kim SY. Clinical values for abnormal-FDG uptake in the head and neck region of patients with head and neck squamous cell carcinoma. Eur J Radiol 2014; 83: 1455-60.
[25] Cheuk DK, Sabin ND, Hossain M, Wozniak A, Naik M, Rodriguez-Galindo C, Krasin MJ, Shulkin BL. PET/CT for staging and follow-up of pediatric nasopharyngeal carcinoma. Eur J Nucl Med Mol Imaging 2012; 39: 1097-106.
[26] Vellayappan BA, Soon YY, Earnest A, Zhang Q, Koh WY, Tham IW, Lee KM. Accuracy of (18) F-flurodeoxyglucose-positron emission tomography/computed tomography in the staging of newly diagnosed nasopharyngeal carcinoma: a systematic review and meta-analysis. Radiol Oncol 2014; 48: 331-8.
[27] van den Brekel MW, Stel HV, Castelijns JA, Nauta JJ, van der Waal I, Valk J, Meyer CJ, Snow GB. Cervical lymph node metastasis: assessment of radiologic criteria. Radiology 1990; 177: 379-384.
[28] Sun R, Tang X, Yang Y, Zhang C. (18)FDG-PET/CT for the detection of regional nodal metastasis in patients with head and neck cancer: a meta-analysis. Oral Oncol 2015; 51: 314-20.
[29] Tantiwongkosi B, Yu F, Kanard A, Miller FR. Role of 18F-FDG PET/CT in pre and post treatment evaluation in head and neck carcinoma. World J Radiol 2014; 6: 177-191.
[30] Castaldi P, Leccisotti L, Bussu F, Micciché F, Rufini V. Role of 18F-FDG PET-CT in head and neck squamous cell carcinoma. Acta Otorhinolaryngol Ital 2013; 33: 1-8.
[31] Shen G, Zhang W, Jia Z, Wang Q, Deng H. Meta-analysis of diagnostic value of 18F-FDG PET or PET/CT for detecting lymph node and distant metastases in patients with nasopharyngeal carcinoma. Br J Radiol 2014; 87: 20140296.
[32] Tang LQ, Chen QY, Fan W, et al. Prospective study of tailoring whole-body dual-modality [18F]fluorodeoxyglucose positron emission tomography/computed tomography with plasma Epstein-Barr virus DNA for detecting distant metastasis in endemic nasopharyngeal carcinoma at initial staging. J Clin Oncol 2013; 31: 2861-9.
[33] Xu GZ, Guan DJ, He ZY. ^{18}F-FDG-PET/CT for detecting distant metastases and second primary cancers in patients with head and neck cancer. A meta-analysis. Oral Oncol 2011; 47: 560-5.
[34] Xu G, Li J, Zuo X, Li C. Comparison of whole body positron emission tomography (PET)/PET-computed tomography and conventional anatomic imaging for detecting distant malignancies in patients with head and neck cancer: a meta-analysis. Laryngoscope 2012; 122: 1974-8.
[35] Yoo J, Henderson S, Walker-Dilks C. Evidence-based guideline recommendations on the use of positron emission tomography imaging in head and neck cancer. Clin Oncol (R Coll Radiol) 2013; 25: e33-66.
[36] Chang MC, Chen JH, Liang JA, Yang KT, Cheng KY, Kao CH. Accuracy of whole-body FDG-PET and FDG-PET/CT in M staging of nasopharyngeal carcinoma: a systematic review and meta-analysis. Eur J Radiol 2013; 82: 366-73.
[37] Lin S, Li X, Wu H, Lu J, Liang B, Peng X, Li S, Yu L, Liu X. Efficiency comparison between PET/CT and conventional work-up for evaluating distant metastasis of nasopharyngeal carcinoma . Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2012; 26: 529-32.

[38] MacManus M, Nestle U, Rosenzweig KE, Carrio I, Messa C, Belohlavek O, Danna M, Inoue T, Deniaud-Alexandre E, Schipani S, Watanabe N, Dondi M, Jeremic B. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006-2007. Radiother Oncol 2009; 91: 85-94.

[39] Gardner M, Halimi P, Valinta D, Plantet MM, Alberini JL, Wartski M, Banal A, Hans S, Floiras JL, Housset M, Labib A. Use of single MRI and 18F-FDG PET-CT scans in both diagnosis and radiotherapy treatment planning in patients with head and neck cancer: advantage on target volume and critical organ delineation. Head Neck 2009; 31: 461-467.

[40] Luis A. Pérez Romasanta, María José García Velloso, Antonio López Medina. Functional imaging in radiation therapy planning for head and neck cancer. Rep Pract Oncol Radiother 2013; 18: 376-382.

[41] Arens AI, Troost EG, Schinagl D, Kaanders JH, Oyen WJ. FDG-PET/CT in radiation treatment planning of head and neck squamous cell carcinoma. Q J Nucl Med Mol Imaging 2011; 55: 521-8.

[42] Kam MK, Wong FC, Kwong DL, Sze HC, Lee AW. Current controversies in radiotherapy for nasopharyngeal carcinoma (NPC). Oral Oncol 2014; 50: 907-12.

[43] Venkada MG, Rawat S, Choudhury P, Rajesh T, Rao S, Khullar P, Kakria A. A quantitative comparison of gross tumour volumes delineated on [18F]-FDG PET-CT scan and CECT scan in head and neck cancers. Indian J Nucl Med 2012; 27: 95-100.

[44] Arslan S, Abakay CD, Sen F, Altay A, Akpinar T, Ekinci AS, Esbah O, Uslu N, Kekilli KE, Ozkan L. Role of PET/CT in treatment planning for head and neck cancer patients undergoing definitive radiotherapy. Asian Pac J Cancer Prev 2014; 15: 10899-10903.

[45] Leclerc M, Lartigau E, Lacornerie T, Daisne JF, Kramar A, Grégoire V. Primary tumor delineation based on (18)FDG PET for locally advanced head and neck cancer treated by chemoradiotherapy. Radiother Oncol 2015; 116: 87-93.

[46] Troost EG, Schinagl DA, Bussink J, Oyen WJ, Kaanders JH. Clinical evidence on PET-CT for radiation therapy planning in head and neck tumours. Radiother Oncol 2010; 96: 328-34.

[47] Wang J, Zheng J, Tang T, Zhu F, Yao Y, Xu J, Wang AZ, Zhang L. A Randomized Pilot Trial Comparing Position Emission Tomography (PET)-Guided Dose Escalation Radiotherapy to Conventional Radiotherapy in Chemoradiotherapy Treatment of Locally Advanced Nasopharyngeal Carcinoma. PLoS One 2015; 10: e0124018.

[48] Law A, Peters LJ, Dutu G, Rischin D, Lau E, Drummond E, Corry J. The utility of PET/CT in staging and assessment of treatment response of nasopharyngeal cancer. J Med Imaging Radiat Oncol 2011; 55: 199-205.

[49] Lin Q, Yang RS, Sun L, Li YM, Wang LC, Dai MM, Luo ZM, Zhao L, Wu H. Serial (18)F-FDG PET-CT imaging during radiotherapy for nasopharyngeal carcinoma: a prospective clinical study. Zhonghua Zhong Liu Za Zhi 2012; 34: 356-9.

[50] Yuan JW, Fen YL, Xian WJ, He XH, Yuan BH, Ye QL. Early monitoring of radiotherapeutic effects of nasopharyngeal carcinoma xenografts in nude mice using18F-FDG PET-CT imaging. Chin J Cancer 2010; 29: 374-8.

[51] Su M, Zhao L, Wei H, Lin R, Zhang X, Zou C. 18F-fluorodeoxyglucose positron emission tomography for predicting tumor response to radiochemotherapy in nasopharyngeal carcinoma. Strahlenther Onkol 2015; 191: 642-648.

[52] Lee AW, Sze WM, Au JS, Leung SF, Leung TW, Chua DT, Zee BC, Law SC, Teo PM, Tung SY, Kwong DL, Lau WH. Treatment results for nasopharyngeal carcinoma in the modern era: the Hong Kong experience. Int J Radiat Oncol Biol Phys 2005; 61: 1107-16.

[53] Shen T, Tang LQ, Luo DH, Chen QY, Li PJ, Mai DM, Guo SS, Liu LT, Qian CN, Guo X, Zeng MS, Mo HY, Mai HQ. Different Prognostic Values of Plasma Epstein-Barr Virus DNA and Maximal Standardized Uptake Value of 18F-FDG PET/CT for Nasopharyngeal Carcinoma Patients with Recurrence. PLoS One 2015; 10: e0122756.

[54] Xiao W, Xu A, Han F, Lin X, Lu L, Shen G, Huang S, Fan W, Deng X, Zhao C. Positron emission tomography-computed tomography before treatment is highly prognostic of distant metastasis in nasopharyngeal carcinoma patients after intensity-modulated radiotherapy treatment: a prospective study with long-term follow-up. Oral Oncol 2015; 51: 363-9.

[55] Hsieh TC, Hsieh CY, Yang TY, Chen TT, Lin CY, Lin CC, Hua CH, Chiu CF, Yeh SP, Sher YP. [18F] Fluorodeoxyglucose Positron Emission Tomography Standardized Uptake Value as a Predictor of Adjuvant Chemotherapy Benefits in Patients With Nasopharyngeal Carcinoma. Oncologist 2015; 20: 539-45.

[56] Sager S, Asa S, Yilmaz M, Uslu L, Vatankulu B, Halaç M, Sönmezoglu K, Kanmaz B. Prognostic significance and predictive performance of volume-based parameters of F-18 FDG PET/CT in squamous cell head and neck cancers. J Cancer Res Ther 2014; 10: 922-6.

[57] Chang KP, Tsang NM, Liao CT, Hsu CL, Chung MJ, Lo CW, Chan SC, Ng SH, Wang HM, Yen TC. Prognostic significance of 18F-FDG PET parameters and plasma Epstein-Barr virus DNA load in patients with nasopharyngeal carcinoma. J Nucl Med 2012; 53: 21-8.

[58] Shi Q, Yang Z, Zhang Y, Hu C. Adding maximum standard uptake value of primary lesion and lymph nodes in 18F-fluorodeoxyglucose PET helps predict distant metastasis in patients with nasopharyngeal carcinoma. PLoS One 2014; 9: e103153.

[59] Yoon YH, Lee SH, Hong SL, Kim SJ, Roh HJ, Cho KS. Prognostic value of metabolic tumor volume as measured by fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography in nasopharyngeal carcinoma. Int Forum Allergy Rhinol 2014; 4: 845-50.

[60] Moon SH, Choi JY, Lee HJ, Son YI, Baek CH, Ahn YC, Ahn MJ, Park K, Kim BT. Prognostic value of volume-based positron emission tomography/computed tomography in patients with nasopharyngeal carcinoma treated with concurrent chemoradiotherapy. Clin Exp Otorhinolaryngol 2015; 8: 142-148.

[61] Huang B, Chan T, Kwong DL, Chan WK, Khong PL. Nasopharyngeal carcinoma: investigation of intratumoral heterogeneity with FDG PET/CT. AJR Am J Roentgenol 2012; 199: 169-74.

[62] Yang Z, Shi Q, Zhang Y, Pan H, Yao Z, Hu S, Shi W, Zhu B, Zhang Y, Hu C Pretreatment 18 F-FDG uptake heterogeneity can predict survival in patients with locally advanced nasopharyngeal carcinoma-a retrospective study. Radiat Oncol 2015; 10: 4.

[63] Shen G, Zhou L, Jia Z, Zhang W, Wang Q, Deng H. Meta-analysis of PET/CT for diagnosis of residual/recurrent nasopharyngeal carcinoma. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2015; 29: 61-7.

[64] Sagardoy T, Fernandez P, Ghafouri A, Digue L, Haaser T, de Clermont-Galleran H, Castetbon V, de Monès E. Accuracy of 18 FDG PET-CT for treatment evaluation 3 months after completion of chemoradiotherapy for head and neck squamous cell carcinoma: 2-year minimum follow-up. Head Neck 2016; 38 Suppl 1: E1271-6.

[65] Sheikhbahaei S, Taghipour M, Ahmad R, Fakhry C, Kiess AP, Chung CH, Subramaniam RM. Diagnostic Accuracy of Follow-Up FDG PET or PET/CT in Patients With Head and Neck Cancer After Definitive Treatment: A Systematic Review and Meta-Analysis. AJR Am J Roentgenol 2015; 205: 629-39.

[66] Chen L, Zhang N, Wang Y, Xian W, Hu W, Wei G. Value of FDG PET-CT associated with pathology in diagnosing residual tumor in patients with nasopharyngeal carcinoma after radiotherapy. Zhonghua Zhong Liu Za Zhi 2015; 37: 213-5.

[67] Shields AF, Grierson JR, Dohmen BM, Machulla HJ, Stayanoff JC, Lawhorn-Crews JM, Obradovich JE, Muzik O, Mangner TJ. Imaging proliferation in vivo with ^{18}F-FLT and positron emission tomography. Nat Med 1998; 4: 1334-1336.

[68] Rasey JS, Grierson JR, Wiens LW, Kolb PD, Schwartz JL. Validation of FLT uptake as a measure of thymidine kinase-1 activity in A549 carcinoma cells. J Nucl Med 2002; 43: 1210-1217.

[69] Zheng Y, Yang Z, Zhang Y, Shi Q, Bao X, Zhang J, Yuan H, Yao Z, Hu C, Zhang Y. The preliminary study of 18F-FLT micro-PET/CT in predicting radiosensitivity of human nasopharyngeal carcinoma xenografts. Ann Nucl Med 2015; 29: 29-36.

[70] Hoeben BA, Troost EG, Span PN, van Herpen CM, Bussink J, Oyen WJ, Kaanders JH. 18 F-FLT PET during radiotherapy or chemoradiotherapy in head and neck squamous cell carcinoma is an early predictor of outcome. J Nucl Med 2013; 54: 532-40.

[71] Hoshikawa H, Mori T, Yamamoto Y, Kishino T, Fukumura T, Samukawa Y, Mori N, Nishiyama Y. Prognostic value comparison between (18) F-FLT PET/CT and (18)F-FDG PET/CT volume-based metabolic parameters in patients with head and neck cancer. Clin Nucl Med 2015; 40: 464-8.

[72] Beheshti M, Imamovic L, Broinger G, Vali R, Waldenberger P, Stoiber F, Nader M, Gruy B, Janetschek G, Langsteger W. 18F choline PET/CT in the preoperative staging of prostate cancer in patients with intermediate or high risk of extracapsular disease: a prospective study of 130 patients. Radiology 2010; 254: 925-933.

[73] Kato T, Shinoda J, Nakayama N, Miwa K, Okumura A, Yano H, Yoshimura S, Maruyama T, Muragaki Y, Iwama T. Metabolic assessment of gliomas using 11C-methionine, [18F] fluorodeoxyglucose, and 11C-choline positron-emission tomography. AJNR 2008; 29: 1176-1182.

[74] Wu HB, Wang QS, Wang MF, Zhen X, Zhou WL, Li HS. Preliminary study of 11C-choline PET/CT for T staging of locally advanced nasopharyngeal carcinoma: comparison with 18F-FDG PET/CT. J Nucl Med 2011; 52: 341-346.

[75] Jiang J, Wu H, Huang M, Wu Y, Wang Q, Zhao J, Yang W, Chen W, Feng Q. Variability of Gross Tumor Volume in Nasopharyngeal Carcinoma Using11C-Choline and 18F-FDG PET/CT. PLoS One 2015; 10: e0131801.

[76] Khor LK, Loi HY, Sinha AK, Tong KT, Goh BC, Loh KS, Lu SJ. ^{68}Ga-DOTA-peptide: A novel molecular biomarker for nasopharyngeal carcinoma. Head Neck 2016; 38: E76-80.

[77] Schartinger VH, Dudms J, Url C, Reinold S, Virgolini IJ, Kroiss A, Riechelmann H, Uprimny C. (68)Ga-DOTA(0)-Tyr (3)-octreotide positron emission tomography in nasopharyngeal carcinoma. Eur J Nucl Med Mol Imaging 2015; 42: 20-4.